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(54) **Cycloalkano[b]dihydroindoles and -indolesulphonamides substituted by heterocycles.**

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EP 0 451 634 B1

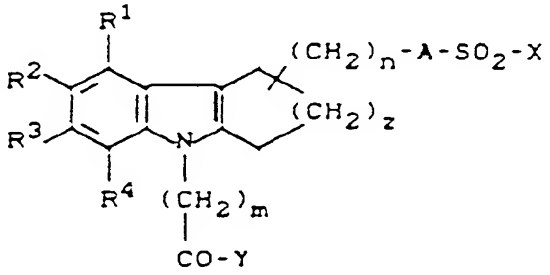
Description

The invention relates to new cycloalkano[b]dihydroindoles and -indolesulphonamides substituted by heterocycles, to processes for their preparation and to their use in medicaments.

It is already known that cycloalkano[b]dihydroindoles and -indolesulphonamides have a thrombocyte aggregation-inhibiting action [compare DOS (German Offenlegungsschrift) 3,631,824].

Furthermore EP 201 735 discloses heterocyclic substituted Indolethane-sulphonamides with thrombocyte aggregation inhibiting properties.

New cycloalkano[b]indolesulphonamides, substituted by heterocycles, of the general formula (I)



(I)

in which

R^1, R^2, R^3 and R^4 are identical or different and

- represent hydrogen, fluorine, chlorine, trifluoromethyl or trifluoromethoxy or straight-chain or branched alkyl having up to 4 carbon atoms,

m - represents the number 1 or 2,

n - represents the number 0 or 1,

z - represents the number 1 or 2,

A - represents the -NH group,

X - represents pyridyl, thienyl, pyrryl, imidazolyl, isothiazolyl or thiazolyl, which are optionally substituted by fluorine, chlorine, bromine, trifluoromethyl, trifluoromethoxy or straight-chain or branched alkyl having up to 4 carbon atoms,

Y - represents hydroxyl, alkoxy having up to 4 carbon atoms, phenoxy or a group of the formula $-NR^6R^7$, in which

R^6 and R^7 are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

if appropriate in an isomeric form, and their salts, have now been found.

The cycloalkano[b]indolesulphonamides substituted by heterocycles, according to the invention, have one or more asymmetric carbon atoms and can therefore exist is various stereochemical forms. Regioisomers may also occur. The invention relates both to the individual isomers and to their mixtures.

The compounds according to the invention exist in stereoisomeric forms which behave either as image and mirror image (enantiomers) or which do not behave as image and mirror image (diastereomers). The invention relates both to the antipodes and to the racemic modifications and the diastereomer mixtures. The racemic modifications, like the diastereomers, can be separated into the stereoisomerically uniform constituents in a known manner (compare E.L. Eliel, Stereochemistry of Carbon Compounds, McGraw Hill, 1962).

The cycloalkano[b]indolesulphonamides substituted by heterocycles, according to the invention, can also be present in the form of their salts. In general, salts with organic or inorganic bases or acids may be mentioned here.

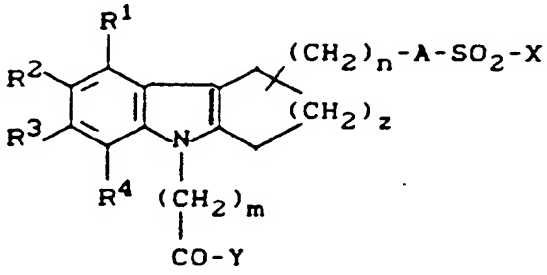
In the context of the present invention, physiologically acceptable salts are preferred. Physiologically acceptable salts of the cycloalkano[b]indolesulphonamides substituted by heterocycles can be metal salts or ammonium salts of the substances according to the invention which have a free carboxyl group. Particularly preferred salts are, for example, sodium, potassium, magnesium or calcium salts, and also ammonium salts which are derived from ammonia or organic amines, such as, for example, ethylamine, di- or triethylamine, di- or triethanolamine, dicyclohexylamine, dimethylaminoethanol, arginine, lysine or ethylenediamine.

Physiologically acceptable salts may also be salts of the compounds according to the invention with inor-

ganic or organic acids. Preferred salts are those with inorganic acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or salts with organic carboxylic or sulphonic acids such as, for example, acetic acid, maleic acid, fumaric acid, malic acid, citric acid, tartaric acid, lactic acid, benzoic acid or methanesulphonic acid, ethanesulphonic acid, phenylsulphonic acid, toluenesulphonic acid or naphthalenedisulphonic acid.

The substances according to the invention surprisingly show a thrombocyte aggregation-inhibiting action, and additionally cause an inhibition of thromboxane synthase in isolated platelets and can be used for the therapeutic treatment of humans and animals.

The compounds of the general formula (I)



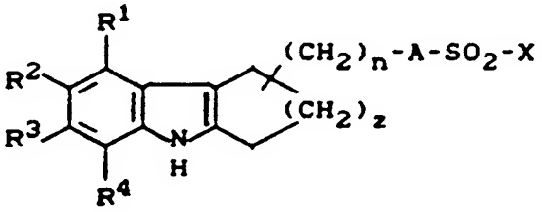
(I)

in which

R^1, R^2, R^3, R^4, A, X, Y, m, n and z have the abovementioned meaning,

can be prepared by a process in which

[A] in the case in which m represents the number 2, compounds of the general formula (II)



(II)

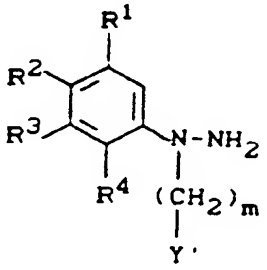
in which

R^1, R^2, R^3, R^4, A, X, n and z have the abovementioned meaning,

are reacted first with acrylonitrile in inert solvents to give the corresponding cyanoethyl compounds, if appropriate in the presence of a base, and then hydrolysed by a customary method to give the corresponding acids (Y=OH),

or by a process in which

[B] compounds of the general formula (III)



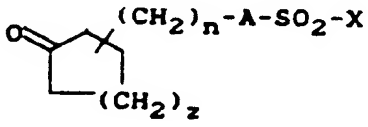
(III)

in which

R^1, R^2, R^3, R^4 and m have the abovementioned meaning, and

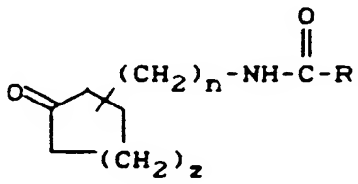
Y' - represents carboxyl, (C_1-C_4)-alkoxycarbonyl or cyano,

are reacted directly with cycloalkanonesulphonamides of the general formula (IV)



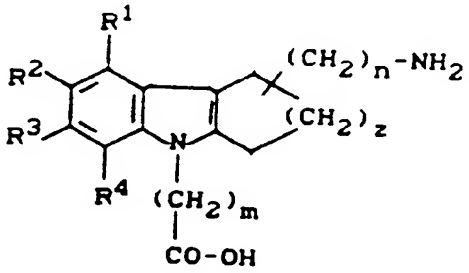
(IV)

in which
z, n, A and X have the abovementioned meaning,
in inert solvents, if appropriate in the presence of a catalyst,
or
[C] compounds of the general formula (III) are reacted first with compounds of the general formula (IVa)



(IVa)

in which
z and n have the abovementioned meaning,
and
R - represents straight-chain or branched (C_1-C_8)-alkyl or phenyl,
with subsequent hydrolysis, to give compounds of the general formula (V)

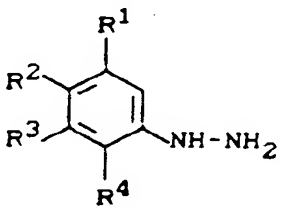


(V)

in which
R^1, R^2, R^3, R^4, m, n and z have the abovementioned meaning,
and in a further step are sulphonated with sulphonyl halides of the general formula (VI)

$$Hal\text{-}SO_2\text{-}X \qquad (VI)$$

in which
X has the abovementioned meaning
and
Hal represents fluorine, chlorine or bromine, preferably chlorine,
[D] or in the case in which m represents the number 2, and A denotes the -NH group,
phenylhydrazines of the general formula (IIIa)



(IIIa)

in which

R^1, R^2, R^3 and R^4 have the abovementioned meaning, are first reacted with the abovementioned compounds of the general formula (IV) or (IVa) and subsequently with acrylonitrile, then the cyanoethyl compounds are hydrolysed to the corresponding carboxylic acids and in the case of the compounds of the general formula (IVa) sulphonated in a further step with the compounds of the general formula (VI) and additionally in the processes [B] and [C] in the case of the acids (Y=OH), the esters or nitriles are hydrolysed by a customary method,

in the case of the variation of the esters (Y = alkoxy, C_1-C_8-phenoxy), the acids are esterified with the appropriate alcohols in the presence of a catalyst according to a customary method, if appropriate in inert solvents,

in the case of the amides and sulphonamides (Y = $-NR^6R^7$, $-NHSO_2-R^5$), either the esters directly or the acids, after customary activation, are reacted with the amines or sulphonamides of the general formulae (VIIa) and (VIIb)

HNR^6R^7 (VIIa) $NH_2-SO_2-R^5$ (VIIb)

in which

R^5, R^6 and R^7 have the abovementioned meaning,

if appropriate in the presence of a catalyst,

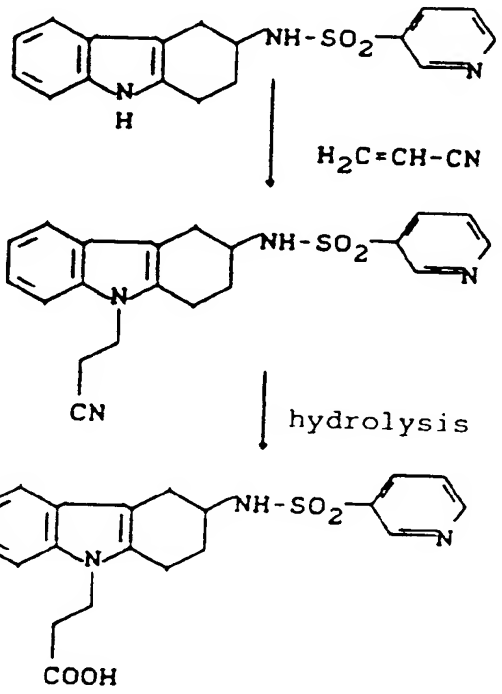
and

if appropriate the isomers are separated and

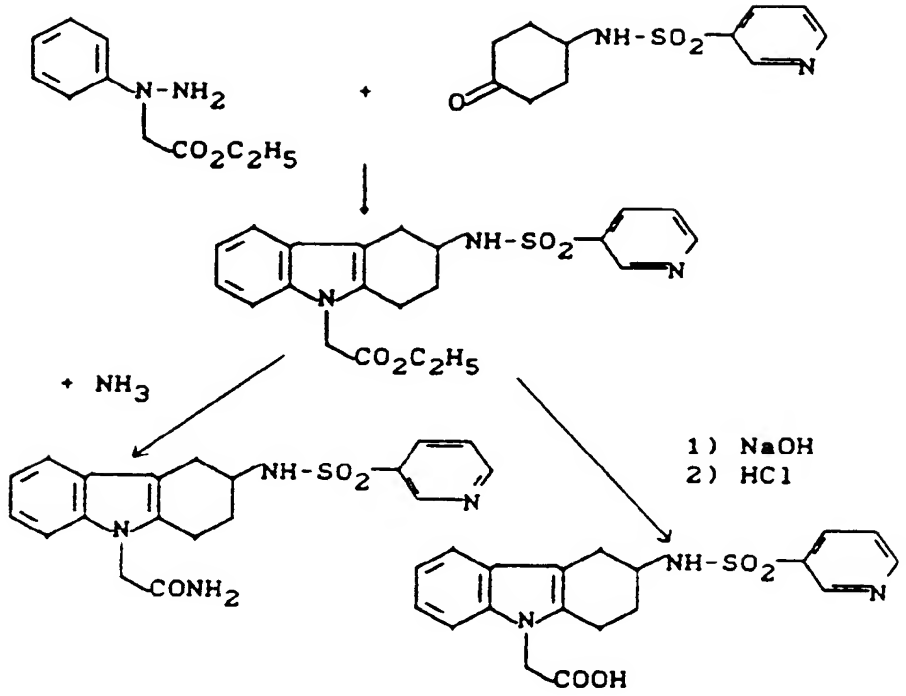
in the case of the preparation of the salts, reacted with an appropriate base or acid.

The processes according to the invention can be illustrated by way of example by the following equations:

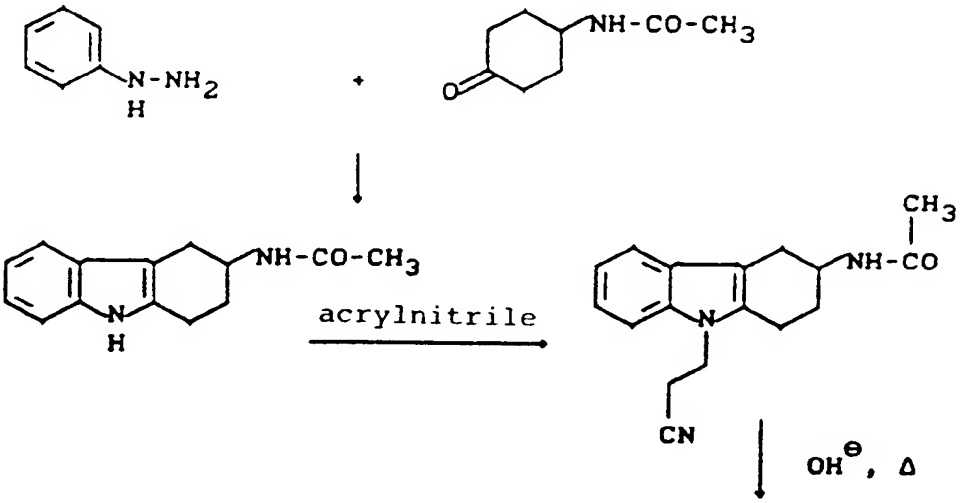
[A]

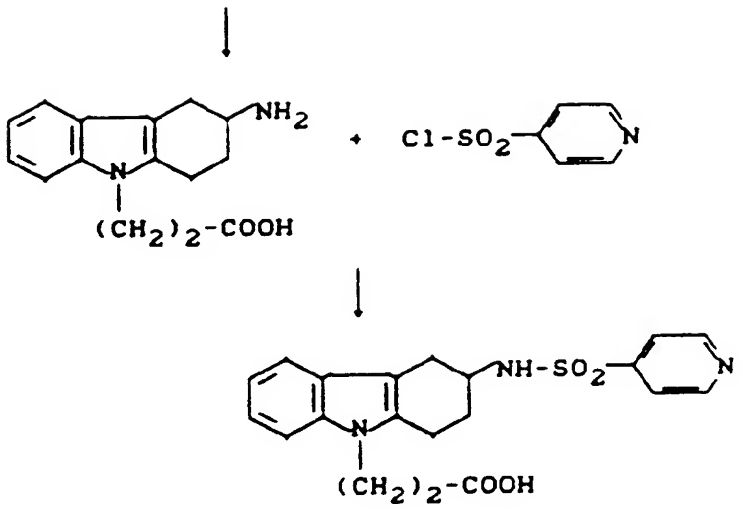


[B]


N-NH2
CO2C2H5
NH-SO2
N
O
+ NH3
CONH2
1) NaOH
2) HCl
COOH

[D]


N-NH2
H
NH-CO-CH3
O
acrylnitrile
CH3
NH-CO
CN
OH⊖, Δ



Possible solvents for processes [A] to [D] according to the invention are water or organic solvents which do not change under the reaction conditions. These preferably include chlorinated hydrocarbons, such as, for example, chloroform or methylene chloride, alcohols such as methanol, ethanol, propanol or isopropanol, ethers such as diethyl ether, tetrahydrofuran, dioxane, glycol monomethyl ether or glycol dimethyl ether, hydrocarbons such as benzene, toluene, xylene, cyclohexane, pentane or mineral oil fractions, dimethyl sulphoxide, dimethyl formamide, hexamethylphosphoramide, ethyl acetate, acetonitrile or pyridine. It is also possible to use mixtures of the solvents mentioned.

Possible bases for processes [A] to [D] according to the invention are customary basic compounds. These preferably include alkali metal hydroxides and alkaline earth metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide or barium hydroxide, alkali metal hydrides such as sodium hydride, alkali metal carbonates or alkaline earth metal carbonates such as sodium carbonate, potassium carbonate, or alkali metal alkoxides such as, for example, sodium methoxide or sodium ethoxide, potassium methoxide, potassium ethoxide or potassium tert.-butoxide or amides such as sodium amide or lithium diisopropylamide, or organic amines or ammonium salts such as benzyltrimethylammonium hydroxide, tetrabutylammonium hydroxide, pyridine, triethylamine or N-methylpiperidine.

Processes [A] to [D] according to the invention are in general carried out in a temperature range from -20°C to +150°C.

In general, processes [A] to [D] are carried out at normal pressure. However, it is also possible to work at elevated pressure or at reduced pressure (for example from 0.5 to 5 bar).

The nitriles are hydrolysed in a manner known per se in water or in one of the abovementioned solvents, such as, for example, ethanol, isopropanol, ethylene glycol or glyme or their mixtures, in the presence of bases, acids, hydrogen peroxide or alkali metal or alkaline earth metal peroxides, if appropriate in catalytic amounts.

Suitable peroxides are, for example, sodium peroxide or barium peroxide.

Suitable bases are alkaline earth metal hydroxides or alkali metal hydroxides, such as, for example, sodium hydroxide, potassium hydroxide or barium hydroxide. Sodium hydroxide is preferred.

Suitable acids are the customary acids. These preferably include inorganic acids such as hydrochloric acid or sulphuric acid.

The hydrolysis of the nitriles is in general carried out in a temperature range from -20°C to +200°C, preferably from +20°C to +150°C.

The esters are hydrolysed by a customary method, by treating the esters in inert solvents with customary bases, it being possible to convert the initially resulting salts into the free carboxylic acids by treating with acid.

Suitable bases for the hydrolysis are the customary inorganic bases. These preferably include alkali metal hydroxides or alkaline earth metal hydroxides such as, for example, sodium hydroxide, potassium hydroxide or barium hydroxide, or alkali metal carbonates such as sodium carbonate or potassium carbonate.

Suitable solvents for the hydrolysis are water or the organic solvents customary for hydrolysis. These preferably include alcohols such as methanol, ethanol, propanol, isopropanol or butanol, or ethers such as tetrahydrofuran or dioxane, or dimethylformamide or dimethyl sulphoxide. Water or alcohols such as methanol, ethanol, propanol or isopropanol are particularly preferably used.

It is also possible to use mixtures of the solvents mentioned.

The hydrolysis is in general carried out in a temperature range from 0°C to +140°C, preferably from +20°C to +100°C.

In general, the hydrolysis is carried out at normal pressure. However, it is also possible to work at elevated pressure or at reduced pressure (for example from 0.5 to 5 bar).

When carrying out the hydrolysis, the base is in general employed in an amount from 1 to 10 moles, preferably from 1 to 5 moles, relative to 1 mole of the ester.

When carrying out the reaction, the carboxylates of the compounds according to the invention are formed in the first step as intermediates which can be isolated. The acids according to the invention are obtained by treating the carboxylates with customary inorganic acids. These preferably include mineral acids such as, for example, hydrochloric acid, hydrobromic acid, sulphuric acid or phosphoric acid. In this connection, it has proved advantageous in the preparation of the carboxylic acids to acidify the basic reaction mixture from the hydrolysis in a second step without isolation of the carboxylates. The acids can then be isolated in a customary manner. In the case of the basic heterocycles, the salts of these heterocycles with the inorganic acids can also be obtained by treating the solutions of the carboxylates with the abovementioned acids.

The acids are esterified according to a customary method, by reacting the acids in the presence of a catalyst with the corresponding alcohols, if appropriate in one of the abovementioned solvents. Preferably, this alcohol is also employed as a solvent.

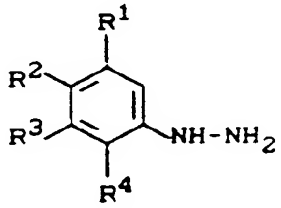
Catalysts which can be employed are inorganic acids, such as, for example, sulphuric acid or inorganic acid chlorides, such as, for example, thionyl chloride.

In general, 0.01 to 1, preferably 0.05 to 0.5 mole of catalyst is employed, relative to 1 mole of reactant.

The amidation is carried out in one of the abovementioned solvents, preferably in alcohols such as ethanol or methanol, in a temperature range from 0°C to +80°C, preferably from +10 to +30°C, and at normal pressure.

Both the esterification and the amidation can proceed via the activated stage of the acid halides (I, Y = halogen), which can be prepared from the corresponding acid by reaction with thionyl chloride, phosphorus trichloride, phosphorus pentachloride, phosphorus tribromide or oxalyl chloride.

The compounds of the general formula (II) are new. They can be prepared by a process in which phenylhydrazines of the general formula (IIIa)

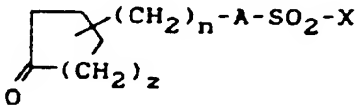


(IIIa)

in which

R^1, R^2, R^3 and R^4 have the abovementioned meaning,

are reacted with cycloalkanonesulphonamides of the general formula (IV)



(IV)

in which

A, X, n and z have the abovementioned meaning,

in analogy to the reaction conditions given under process [B].

Hydrazines which are employed for the process are, for example: phenylhydrazine, 4-methoxyphenylhydrazine, 4-chlorophenylhydrazine, 4-fluorophenylhydrazine, 4-methylphenylhydrazine, 2,4-difluorophenylhydrazine, 3,5-difluorophenylhydrazine, 3-fluorophenylhydrazine and 2-fluorophenylhydrazine.

The phenylhydrazines of the general formulae (III) and (IIIa) are known in some cases or can be prepared by a customary method [compare Houben-Weyl, "Methoden der organischen Chemie" (Methods of Organic Chemistry) X/2, page 1, 123, 693; DOS 2,312,256].

The enantiomerically pure compounds of the general formula (I) according to the invention can be obtained according to customary methods, for example in analogy to the process described in DOS 3,631,824. The reduction of the cycloalkano[b]indolesulphonamides is also described there.

The cycloalkanonesulphonamides of the general formula (IV) are new and can be prepared, however, just like the known cycloalkanonecarbamides of the formula (IVa) according to the process published in DOS 3,631,824.

The sulphonyl halides of the formula (VI) can be prepared by methods which are known per se [compare Z. Talik and E. PXlazek, Acta Polon. Pharm., 12, 5 (1955)].

The amines of the general formula (VIIa) are known (compare Houben-Weyl, "Methoden der organischen Chemie" (Methods of Organic Chemistry), Vol. XI/1 and XI/2].

The sulphonamides of the general formula (VIIb) are also known [compare Beilstein, 11, 26].

The cycloalkano[b]indolesulphonamides substituted by heterocycles, their salts and isomers can be employed as active compounds in medicaments. The substances have a thrombocyte aggregation-inhibiting and thromboxane A2-antagonistic action and inhibit thromboxane synthase in isolated platelets. They can be employed for the treatment of thromboembolic disorders and ischaemias such as myocardial infarct, stroke, transitory and ischaemic attacks, angina pectoris, peripheral circulatory disorders, prevention of restenoses such as after thrombolytic therapy, percutaneous transluminal angioplasty (PTA), percutaneous transluminal coronary angioplasty (PTCA), bypass and for the treatment of arteriosclerosis, asthma and allergies.

To determine the thrombocyte aggregation-inhibiting action, blood from healthy subjects of both sexes was used. 3.8% strength aqueous sodium citrate solution was admixed to 9 parts of blood as an anticoagulant. Platelet-rich citrate plasma (PRP)[1] was obtained from this blood by means of centrifugation (Jürgens/Beller, Klinische Methoden der Blutgerinnungsanalyse (Clinical Methods of Blood Coagulation Analysis); Thieme Verlag, Stuttgart, 1959).

For these investigations, 0.8 ml of (PRP)[1] and 0.1 ml of the active compound solution were preincubated in the water bath at 37°C. The thrombocyte aggregation was then determined by the turbidometric method (Born, G.V.R., J. Physiol, (London), 162, 67, 1962) in an aggregometer at 37°C (Therapeutische Berichte 47, 80-86, 1975). For this purpose, 0.1 ml of collagen, an aggregation-inducing agent, was added to the preincubated sample. The change of the optical density in the sample of the (PRP) was recorded for a period of 6 minutes and the deflection determined after 6 minutes. For this purpose, the percentage inhibition compared to the control was calculated.

The range of the minimum effective concentration was given as the threshold concentration.

Example No.	TAI threshold concentration µg/ml)
7	0.01 - 0.03
8	0.1 - 0.3
9	0.03 - 0.1
10	0.03 - 0.1
11	0.003 - 0.01
12	0.1 - 0.3

Measurement of thromboxane synthase in washed human thrombocytes.

1. Preparation of thrombocyte suspensions

Blood from healthy donors is taken up in EDTA (1% in 0.9% NaCl, 9 + 1) and centrifuged at 1,000 rpm (150 g) for 20 min. The platelet-rich plasma (PRP)[2] is siphoned off and in each case 10 ml is centrifuged at 2,500 rpm for 20 min. The platelet6rich plasma[2] is decanted off. The remaining platelets are suspended in 5 ml of resuspension buffer (0.15 M TRIS / 0.9% NaCl/ 77 mmol EDTA, 8:91:1; adjusted to pH 7.4 with 1 N HCl), centrifuged at 2,500 rpm for 20 min and suspended in 1 ml of resuspension buffer. The thrombocyte number is adjusted to 3 x 10^5/µl.

2. Measurement of the thromboxane synthase

1 ml of the platelet suspension and 0.01 ml of the test preparation in 10% DMSO are incubated at 37°C for 2 min. 0.1 ml of ^{3}H-arachidonic acid from Amersham Buchler GmbH and Co. KG (6.6×10^{-5} mol/l) having

a specific activity of 140 MBq/mmol are added to this and the mixture is incubated at 37°C for a further 10 min. After the reaction, the mixture is acidified with about 0.02 ml of 0.5 N citric acid and immediately extracted 3 times with 1 ml portions of ethyl acetate. The supernatants are collected in 10 ml glass tubes and the ethyl acetate is blown off at 25°C under N_2. The residue is taken up in 50 µl of MeOH/$CHCl_3$ (1:1) and applied to glass TLC plates (silica gel 60, F254, 20 x 20 cm, Merck).

Separation is carried out in an eluant mixture of $CHCl_3$/MeOH/glacial acetic acid/H_2O (80:8:1:0.8). The distribution of the radioactivity is detected in a Ramona-Ls TLC scanner from Raytest and quantitatively interpreted using an integration programme.

The concentration of the test substances which leads to a 50% inhibition of thromboxane formation compared to the control is determined.

Inhibition of the thromboxane synthase in washed platelets from human blood.

Thromboxane receptor binding test in human thrombocyte membranes

a) Membrane preparation

The blood taken the evening before by standard methods was centrifuged at 10°C and 2,800 rpm for 10 min in the morning. 10 µM indomethacin was added to the Buffy coat resulting in the course of this as a layer between the platelet-poor plasma and the erythrocytes. A preparation of thrombocyte membranes was made from the Buffy coat by a method which has been described by Barber and Jamieson (compare Barber, A.J., Jamieson, G.A.: Isolation and characterization of plasma membranes from human blood platelets, J. Biol. Chem. 245, 6357-6365, 1970). As the most important step, thrombocytes are loaded with glycerol in the course of this and brought to lysis by means of osmotic shock.

The washed membranes thus obtained were resuspended in tris-NaCl-glucose buffer (50 mM tris, 100 mM NaCl, 5 mM glucose, pH 7.4), rapidly frozen in dry ice and stored at -70°C.

b) Displacement studies

For the displacement studies, 100 µg of membrane protein and about 5 nM of ^{3}H-(3R)-3-(4-fluorophenylsulphonamido)-9-(2-carboxyethyl)-1,2,3,4-tetrahydro-4a,4β-carbazole [for preparation compare DOS 3,631,824; the radioactive labelling is carried out by a method known from the literature] were incubated in a total volume of 1 ml of tris-NaCl-glucose buffer. Increasing concentrations of the displacing non-labelled compounds according to the invention dissolved in DMSO were added to the starting mixture (final concentration, 0.5% DMSO, relative to the assay volume).

The substance concentration IC_{50}, which is required in order to displace 50% of the specific binding, was determined with the aid of a logit-log plot according to HILL. The inhibition constant K_I was determined from the IC_{50} and the dissociation constants K_D (determined by Scatchard analysis).

The present invention also includes pharmaceutical preparations which contain one or more compounds of the general formula (I), or which consist of one or more active compounds of the formula (I) in addition to inert, non-toxic, pharmaceutically suitable auxiliaries and excipients, and a method for the production of these preparations.

The active compounds of the formula (I) are intended to be present in these preparations in a concentration of 0.1 to 99.5% by weight, preferably of 0.5 to 95% by weight of the total mixture.

In addition to the active compounds of the formula (I), the pharmaceutical preparations may also contain other pharmaceutical active compounds.

The abovementioned pharmaceutical preparations can be prepared in a customary manner by known methods, for example with the auxiliary (auxiliaries) or excipient(s).

In general, it has proved advantageous to administer the active compound(s) of the formula (I) in total amounts of about 0.03 to about 30 mg/kg, preferably to about 5 mg/kg of body weight every 24 hours, if appropriate in the form of several individual doses, to attain the desired result.

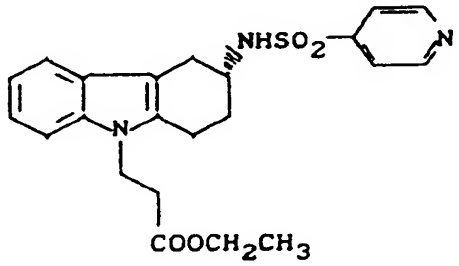
An individual dose contains the active compound(s), preferably in amounts of 0.01 to about 10, particularly preferably 0.1 to 1.0 mg/kg of body weight.

However, it may be advantageous to deviate from the amounts mentioned, in particular depending on the type and the body weight of the subject to be treated, on individual behaviour towards the medicaments, the type and severity of the disorder, the type of preparation and administration, and the time or interval at which administration takes place.

Preparation Examples

Example 1

9-(2-Ethoxycarbonylethyl)-3(R)-(4-pyridylsulphonamido)-1,2,3,4-tetrahydrocarbazole

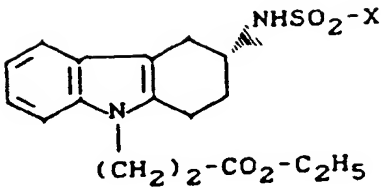


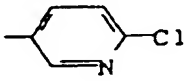
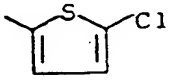
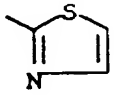
0.9 g (2.3 mmol) of 9-(2-carboxyethyl)-3(R)-(4-pyridylsulphonamido)-1,2,3,4-tetrahydrocarbazole is dissolved in 50 ml of ethanol p.a., 3 ml of concentrated sulphuric acid are added and the mixture is boiled under reflux for 1.5 hours with stirring. After cooling to room temperature, 12.0 g of sodium hydrogen carbonate are added, water is added after the evolution of gas has ended and the mixture is extracted several times with ethyl acetate. The combined organic phases are dried with sodium sulphate and the solvent evaporated therefrom. The crude product is purified by chromatography on silica gel 60 (40-63 µm, Merck, eluant: CH_2Cl_2 : CH_3OH = 10:1).

R_f = 0.63 (CH_2Cl_2 : CH_3OH = 10:1)

The examples shown in Table 1 are prepared in analogy to the procedure of Example 1:

Table 1



Example No.	X	R_f	Eluant
2		0.60	a)
3		0.78	a)
4		0.47	b)
5		0.40	c)
6		0.73	d)

Eluant systems:

a) Toluene/ethyl acetate = 1:1

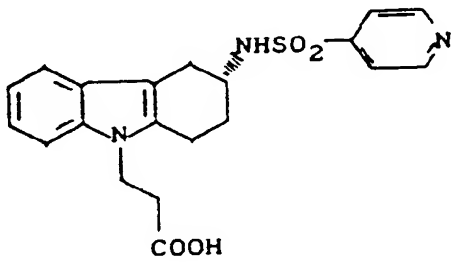
b) Methylene chloride:methanol = 100:1

c) Toluene:ethyl acetate = 2:1

d) Methylene chloride:methanol = 10:1

Example 7

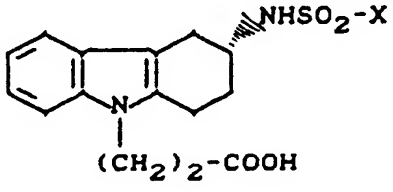
9-(2-Carboxyethyl)-3(R)-(4-pyridylsulphonamido)-1,2,3,4-tetrahydrocarbazole

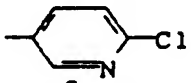
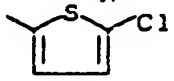
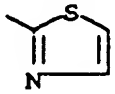
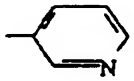


1.3 g (3.4 mmol) of 9-(2-cyanoethyl)-3(R)-(4-pyridylsulphonylamino)-1,2,3,4-tetrahydrocarbazole are dissolved in 10 ml of ethanol, 80 ml of 10% strength sodium hydroxide solution are added and the mixture is heated to reflux for 5 hours. It is then cooled to room temperature and extracted with dichloromethane. After the removal of residual organic solvent from the aqueous phase in vacuo, the solution is cooled to 0°C and acidified to pH = 2 with hydrochloric acid, and the product obtained is filtered off with suction and washed several times with water. The product is dried in a high vacuum over phosphorus pentoxide and sodium hydroxide and purified by chromatography (silica gel 60, 40-63 µm, Merck, eluant: CH_2Cl_2 : CH_3OH = 10:1)
R_f = 0.30 (CH_2Cl_2 = CH_3OH = 10:1)

The examples shown in Table 2 are prepared in analogy to the procedure of Example 6:

Table 2



Example No.	X	R_f	Eluant
8		0.32	e)
9		0.23	e)
10		0.08	e)
11		0.36	e)
12		0.22	e)

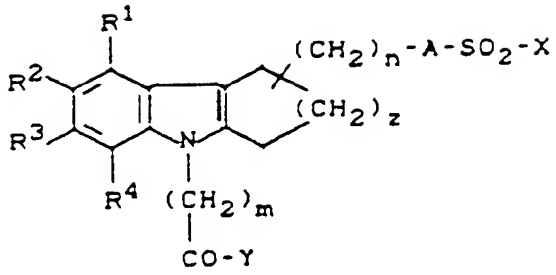
Eluants:

e) Methylene chloride:methanol = 10:1

Claims

Claims for the following Contracting States : DE, GB, FR, IT, NL, SE, CH, BE, AT, LU, GR, DK

1. Cycloalkano[b]indolesulphonamides substituted by heterocycles of the formula



(I)

in which

R^1, R^2, R^3 and R^4 are identical or different and

- represent hydrogen, fluorine, chlorine, trifluoromethyl or trifluoromethoxy or straight-chain or branched alkyl having up to 4 carbon atoms,

m - represents the number 1 or 2,

n - represents the number 0 or 1,

z - represents the number 1 or 2,

A - represents the -NH group,

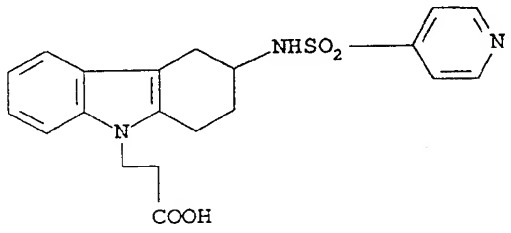
X - represents pyridyl, thienyl, pyrryl, imidazolyl, isothiazolyl or thiazolyl, which are optionally substituted by fluorine, chlorine, bromine, trifluoromethyl, trifluoromethoxy or straight-chain or branched alkyl having up to 4 carbon atoms,

Y - represents hydroxyl, alkoxy having up to 4 carbon atoms, phenoxy or a group of the formula $-NR^6R^7$, in which

R^6 and R^7 are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

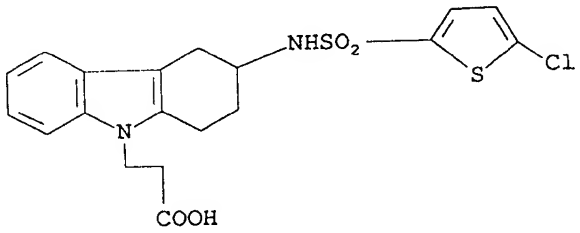
if appropriate in an isomeric form, and their salts.

2. 9-(2-Carboxyethyl)-(4-pyridylsulphonamido)-1,2,3,4-tetrahydrocarbazole of the formula



if appropriate in an isomeric form and salts thereof.

3. 9-(2-Carboxyethyl)-(5-chloro-thiophene-2-yl-sulphonamido)-1,2,3,4-tetrahydrocarbazole of the formula

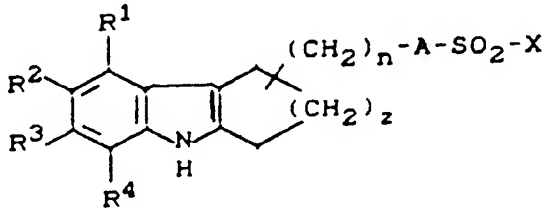


if appropriate in an isomeric form and salts thereof.

4. Cycloalkano[b]indolesulphonamides, substituted by heterocycles, according to Claim 1 to 3 for combating diseases.

5. Process for the preparation of cycloalkano[b]indolesulphonamides, substituted by heterocycles according to claim 1 to 3, if appropriate in an isomeric form, and their salts, characterized in that

[A] in the case in which m represents the number 2, compounds of the general formula (II)



(II)

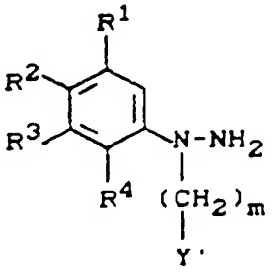
in which

R^1, R^2, R^3, R^4, A, X, n and z have the meaning given in claims 1 - 3,

are reacted first with acrylonitrile in inert solvents to give the corresponding cyanoethyl compounds, if appropriate in the presence of a base, and then hydrolysed by a customary method to give the corresponding acids (Y=OH),

or by a process in which

[B] compounds of the general formula (III)



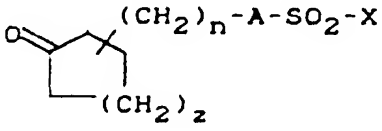
(III)

in which

R^1, R^2, R^3, R^4 and m have the meaning given in claims 1 - 3,

Y' - represents carboxyl, (C_1-C_4)-alkoxycarbonyl or cyano,

are reacted directly with cycloalkanone sulphonamides of the general formula (IV)



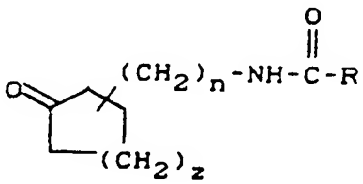
(IV)

in which

z, n, A and X have the meaning given in claims 1 - 3, in inert solvents, if appropriate in the presence of a catalyst,

or

[C] compounds of the general formula (III) are reacted first with compounds of the general formula (IVa)



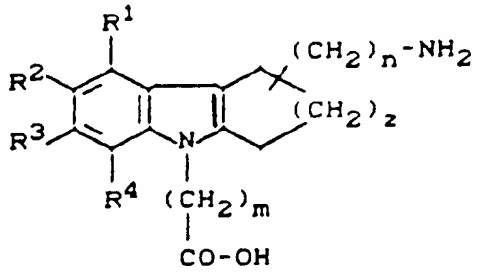
(IVa)

in which

z and n have the meaning given in claims 1 - 3, and

R - represents straight-chain or branched (C_1-C_8)-alkyl or phenyl,

with subsequent hydrolysis, to give compounds of the general formula (V)



(V)

in which

R^1, R^2, R^3, R^4, m, n and z have the meaning given in claims 1 to 3,

and in a further step are sulphonated with sulphonyl halides of the general formula (VI)

$$Hal\text{-}SO_2\text{-}X \qquad (VI)$$

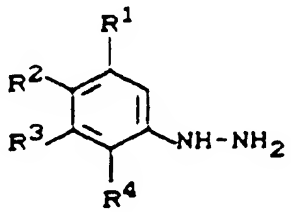
in which

X has the meaning given in claims 1 to 3,

and

Hal represents fluorine, chlorine or bromine, preferably chlorine,

[D] or in the case in which m represents the number 2, and A denotes the -NH group, phenylhydrazines of the general formula (IIIa)



(IIIa)

in which

R^1, R^2, R^3 and R^4 have the meaning given in claims 1 to 3,

are first reacted with the abovementioned compounds of the general formula (IV) or (IVa) and subsequently with acrylonitrile, then the cyanoethyl compounds are hydrolysed to the corresponding carboxylic acids and in the case of the compounds of the general formula (IVa) sulphonated in a further step with the compounds of the general formula (VI) and additionally in the processes [B] and [C] in the case of the acids (Y=OH), the esters or nitriles are hydrolysed by a customary method,

in the case of the variation of the esters (Y = alkoxy, C_1-C_8-phenoxy), the acids are esterified with the appropriate alcohols in the presence of a catalyst according to a customary method, if appropriate in inert solvents,

in the case of the amides and sulphonamides (Y = $-NR^6R^7$, $-NHSO_2$-R^5), either the esters directly or the acids, after customary activation, are reacted with the amines or sulphonamides of the general formulae (VIIa) and (VIIb)

$$HNR^6R^7 \qquad (VIIa) \qquad NH_2\text{-}SO_2\text{-}R^5 \qquad (VIIb)$$

in which

R^5, R^6 and R^7 have the abovementioned meaning,

if appropriate in the presence of a catalyst,

and

if appropriate the isomers are separated and in the case of the preparation of the salts, reacted with an appropriate base or acid.

6. Medicaments containing at least one cycloalkano[b]indolesulphonamide, substituted by heterocycles, ac-

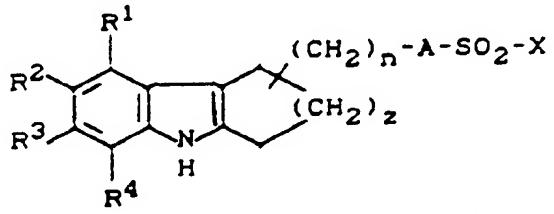
cording to claims 1 to 3.

7. Process for the preparation of a medicament according to claim 6, characterized in that compounds according to claims 1 to 3 are brought into a suitable form for administration, if appropriate with the aid of auxiliaries and excipients.

8. Use of cycloalkano[b]indolesulphonamides, substituted by heterocycles, according to claims 1 to 3 for the production of medicaments.

9. Use of cycloalkano[b]indolesulphonamides, substituted by heterocycles, according to claims 1 to 3 for the production of medicaments for the treatment of thromboembolic disorders, ischaemias, arteriosclerosis, asthma and allergies.

10. Compounds of the general formula

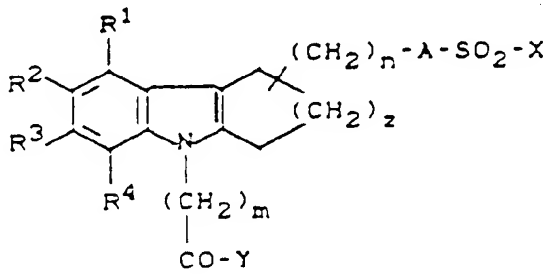


in which
R^1, R^2, R^3 and R^4 are identical or different and
- represent hydrogen, fluorine, chlorine, trifluoromethyl or trifluoromethoxy or straight-chain or branched alkyl having up to 4 carbon atoms,

n - represents the number 0 or 1,
A - represents the -NH group,
X - represents pyridyl, thienyl, pyrryl, imidazolyl, isothiazolyl or thiazolyl, which are optionally substituted by fluorine, chlorine, bromine, trifluoromethyl, trifluoromethoxy or straight-chain or branched alkyl having up to 4 carbon atoms,
Y - represents hydroxyl, alkoxy having up to 4 carbon atoms, phenoxy or a group of the formula -NR^6R^7,
in which
R^6 and R^7 are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,
if appropriate in an isomeric form, and their salts.

Claim for the following Contracting State : ES

1. Process for the preparation of cycloalkano[b]indolesulphonamides substituted by heterocycles of the general formula



(I)

in which
R^1, R^2, R^3 and R^4 are identical or different and

- represent hydrogen, fluorine, chlorine, trifluoromethyl or trifluoromethoxy or straight-chain or branched alkyl having up to 4 carbon atoms,

m - represents the number 1 or 2,

n - represents the number 0 or 1,

z - represents the number 1 or 2,

A - represents the -NH group,

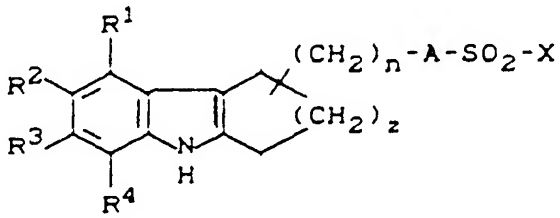
X - represents pyridyl, thienyl, pyrryl, imidazolyl, isothiazolyl or thiazolyl, which are optionally substituted by fluorine, chlorine, bromine, trifluoromethyl, trifluoromethoxy or straight-chain or branched alkyl having up to 4 carbon atoms,

Y - represents hydroxyl, alkoxy having up to 4 carbon atoms, phenoxy or a group of the formula $-NR^6R^7$, in which

R^6 and R^7 are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

if appropriate in an isomeric form, and their salts, characterized in that

[A] in the case in which m represents the number 2, compounds of the general formula (II)



(II)

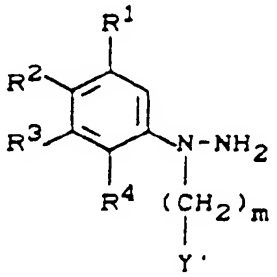
in which

R^1, R^2, R^3, R^4, A, X, n and z have the abovementioned meaning,

are reacted first with acrylonitrile in inert solvents to give the corresponding cyanoethyl compounds, if appropriate in the presence of a base, and then hydrolysed by a customary method to give the corresponding acids (Y=OH),

or by a process in which

[B] compounds of the general formula (III)



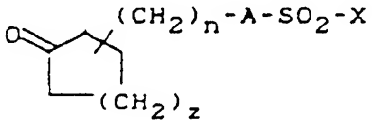
(III)

in which

R^1, R^2, R^3, R^4 and m have the abovementioned meaning,

Y' - represents carboxyl, $(C_1$-$C_4)$-alkoxycarbonyl or cyano,

are reacted directly with cycloalkanone sulphonamides of the general formula (IV)



(IV)

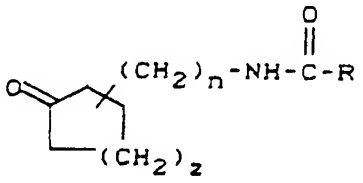
in which

z, n, A and X have the abovementioned meaning, in inert solvents, if appropriate in the presence of a catalyst,

or

[C] compounds of the general formula (III)

are reacted first with compounds of the general formula (IVa)



(IVa)

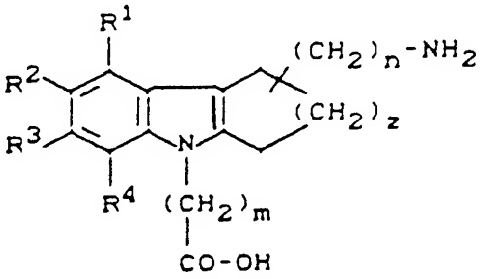
in which

z and n have the abovementioned meaning,

and

R - represents straight-chain or branched (C_1-C_8)-alkyl or phenyl,

with subsequent hydrolysis, to give compounds of the general formula (V)



(V)

in which

R^1, R^2, R^3, R^4 and m, n and z have the abovementioned meaning,

and in a further step are sulphonated with sulphonyl halides of the general formula (VI)

$$Hal\text{-}SO_2\text{-}X \qquad (VI)$$

in which

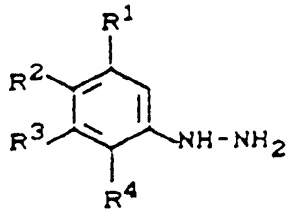
X has the abovementioned meaning,

and

Hal represents fluorine, chlorine or bromine, preferably chlorine,

[D] or in the case in which m represents the number 2, and A denotes the -NH group,

phenylhydrazines of the general formula (IIIa)



(IIIa)

in which

R^1, R^2, R^3, and R^4 have the abovementioned meaning,

are first reacted with the abovementioned compounds of the general formula (IV) or (IVa) and subsequently with acrylonitrile, then the cyanoethyl compounds are hydrolysed to the corresponding carboxylic acids and in the case of the compounds of the general formula (IVa) sulphonated in a further step with the compounds of the general formula (VI) and additionally in the processes [B] and [C] in the case of the acids (Y=OH), the esters or nitriles are hydrolysed by a customary method,

in the case of the variation of the esters (Y = alkoxy, C_1-C_8-phenoxy), the acids are esterified

with the appropriate alcohols in the presence of a catalyst according to a customary method, if appropriate in inert solvents,

in the case of the amides and sulphonamides ($Y = -NR^6R^7$, $-NHSO_2-R^5$), either the esters directly or the acids, after customary activation, are reacted with the amines or sulphonamides of the general formulae (VIIa) and (VIIb)

$$HNR^6R^7 \quad \text{(VIIa)} \qquad NH_2-SO_2-R^5 \quad \text{(VIIb)}$$

in which

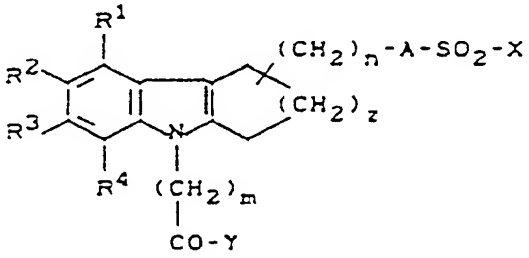
R^5, R^6 and R^7 have the abovementioned meaning, if appropriate in the presence of a catalyst, and

if appropriate the isomers are separated and in the case of the preparation of the salts, reacted with an appropriate base or acid.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, GR, IT, LU, NL, SE

1. Durch Heterocyclen substituierte Cycloalkano[b]indol sulfonamide der Formel



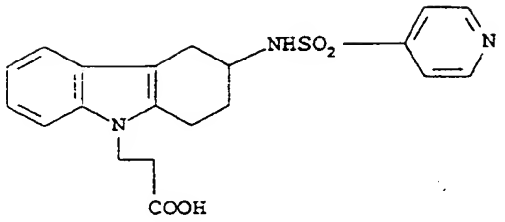
(I)

worin

R^1, R^2, R^3 und R^4	gleich oder verschieden sind und Wasserstoff, Fluor, Chlor, Trifluormethyl oder Trifluormethoxy oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoff-Atomen darstellen,
m	die Zahl 1 oder 2 darstellt,
n	die Zahl 0 oder 1 darstellt,
z	die Zahl 1 oder 2 darstellt,
A	die Gruppe -NH darstellt,
X	Pyridyl, Thienyl, Pyrryl, Imidazolyl, Isothiazolyl oder Thiazolyl darstellt, die gegebenenfalls durch Fluor, Chlor, Brom, Trifluormethyl, Trifluormethoxy oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoff-Atomen substituiert sind,
Y	Hydroxyl, Alkoxy mit bis zu 4 Kohlenstoff-Atomen, Phenoxy oder eine Gruppe der Formel $-NR^6R^7$ darstellt, in der R^6 oder R^7 gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoff-Atomen bezeichnen,

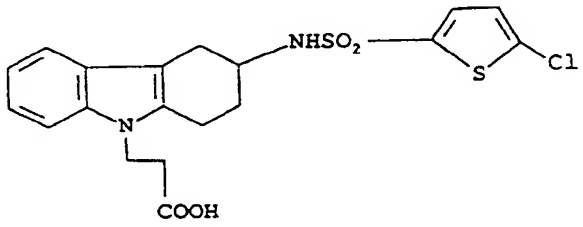
gegebenenfalls in isomerer Form,
und deren Salze.

2. 9-(2-Carboxyethyl)-(4-pyridylsulfonamido)-1,2,3,4-tetrahydrocarbazol der Formel



gegebenenfalls in isomerer Form, und dessen Salze.

3. 9-(2-Carboxyethyl)-(5-chlorthiophen-2-ylsulfonamido) 1,2,3,4-tetrahydrocarbazol der Formel

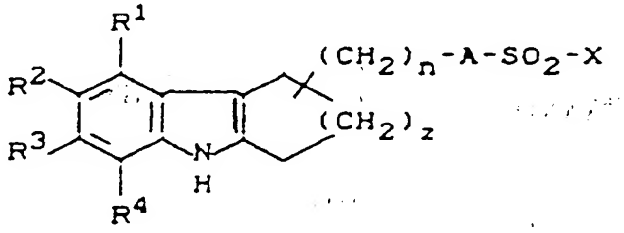


gegebenenfalls in isomerer Form, und dessen Salze.

4. Durch Heterocyclen substituierte Cycloalkano[b]indolsulfonamide nach Anspruch 1 bis 3 zur Bekämpfung von Krankheiten.

5. Verfahren zur Herstellung von Cycloalkano[b]indolsulfonamiden, die durch Heterocyclen substituiert sind, nach Anspruch 1 bis 3, gegebenenfalls in isomerer Form, und der Salze derselben, dadurch gekennzeichnet, daß

[A] in dem Fall, in dem m die Zahl 2 darstellt, Verbindungen der allgemeinen Formel (II)



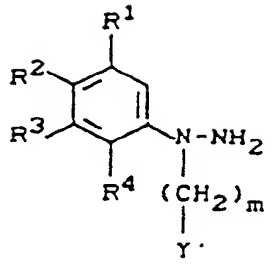
(II)

worin

R^1, R^2, R^3, R^4, A, X, n und z die in den Ansprüchen 1 bis 3 angegebenen Bedeutungen haben,

zuerst mit Acrylnitril in inerten Lösungsmitteln zu den entsprechenden Cyanethyl-Verbindungen, gegebenenfalls in Gegenwart einer Base, umgesetzt werden und dann die Produkte nach einer gängigen Verfahrensweise zu den entsprechenden Säuren (Y = OH) hydrolysiert werden; oder

[B] Verbindungen der allgemeinen Formel (III)



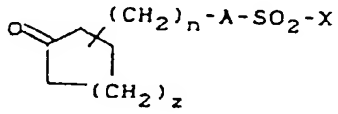
(III)

worin

R^1, R^2, R^3, R^4 und m die in den Ansprüchen 1 bis 3 angegebenen Bedeutungen haben und

Y' Carboxyl, (C_1-C_4)-Alkoxycarbonyl oder Cyan darstellt,

direkt mit Cycloalkanonsulfonamiden der allgemeinen Formel (IV)

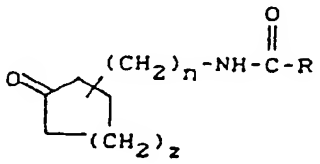


(IV)

worin

z, n, A und X die in den Ansprüchen 1 bis 3 angegebenen Bedeutungen haben, in inerten Lösungsmitteln, gegebenenfalls in Gegenwart eines Katalysators, umgesetzt werden, oder

[C] Verbindungen der allgemeinen Formel (III) zuerst mit Verbindungen der allgemeinen Formel (IVa)



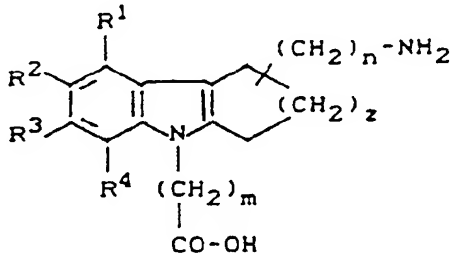
(IVa)

worin

z und n die in den Ansprüchen 1 bis 3 angegebenen Bedeutungen haben und

R geradkettiges oder verzweigtes (C_1-C_8)-Alkyl oder Phenyl darstellt,

umgesetzt werden, wonach Hydrolyse zu Verbindungen der allgemeinen Formel (V)



(V)

erfolgt, worin

R^1, R^2, R^3, R^4, m, n und z die in den Ansprüchen 1 bis 3 angegebenen Bedeutungen haben,

und in einem weiteren Schritt mit Sulfonylhalogeniden der allgemeinen Formel (VI)

$$Hal\text{-}SO_2\text{-}X \qquad (VI),$$

worin

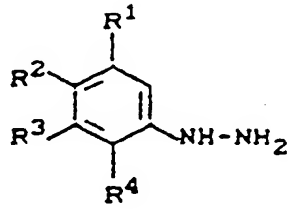
X die in den Ansprüchen 1 bis 3 angegebenen Bedeutungen hat und

Hal Fluor, Chlor oder Brom, vorzugsweise Chlor, darstellt,

sulfoniert werden, oder

[D] in dem Fall, in dem m die Zahl 2 darstellt und A die Gruppe -NH bezeichnet,

Phenylhydrazine der allgemeinen Formel (IIIa)



(IIIa)

worin

R^1, R^2, R^3 und R^4 die in den Ansprüchen 1 bis 3 angegebenen Bedeutungen haben,

zuerst mit den obenerwähnten Verbindungen der allgemeinen Formeln (IV) oder (IVa) und anschließend mit Acrylnitril umgesetzt werden, dann die Cyanethyl-Verbindungen zu den entsprechenden Carbonsäuren hydrolysiert werden und im Fall der Verbindungen der allgemeinen Formel (IVa) in einem weiteren Schritt mit den Verbindungen der allgemeinen Formel (VI) sulfoniert werden

und zusätzlich in den Verfahren [B] und [C] im Fall der Säuren (Y = OH) die Ester oder Nitrile nach einer gängigen Verfahrensweise hydrolysiert werden,

im Fall der Variationen der Ester (Y = Alkoxy, C_1-C_8-Phenoxy) die Säuren mit den geeigneten Alkoholen in Gegenwart eines Katalysators nach einer gängigen Verfahrensweise, gegebenenfalls in inerten Lösungsmitteln, verestert werden,

im Fall der Amide und Sulfonamide (Y = $-NR^6R^7$, $-NHSO_2-R^5$) entweder die Ester direkt oder die Säuren, nach üblicher Aktivierung, mit den Aminen oder Sulfonamiden der allgemeinen Formeln (VIIa) und (VIIb)

HNR^6R^7 (VIIa), $NH_2-SO_2-R^5$ (VIIb),

worin

R^5, R^6 und R^7 die oben erwähnten Bedeutungen haben, gegebenenfalls in Gegenwart eines Katalysators, umgesetzt werden und

gegebenenfalls die Isomeren getrennt werden und im Fall der Herstellung der Salze mit einer geeigneten Base oder Säure umgesetzt werden.

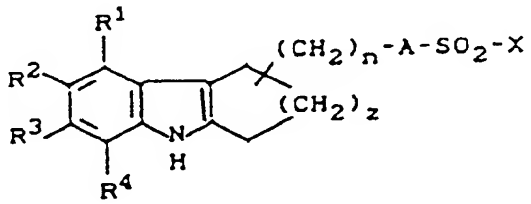
6. Medikamente, enthaltend wenigstens ein durch Heterocyclen substituiertes Cycloalkano[b]indolsulfonamid nach Anspruch 1 bis 3.

7. Verfahren zur Herstellung eines Medikaments nach Anspruch 6, dadurch gekennzeichnet, daß Verbindungen nach Anspruch 1 bis 3 in eine für die Verabreichung geeignete Form gebracht werden, gegebenenfalls unter Mithilfe von Hilfsstoffen und Streckmitteln.

8. Verwendung von Cycloalkano[b]indolsulfonamiden, die durch Heterocyclen substituiert sind, nach Anspruch 1 bis 3 zur Herstellung von Medikamenten.

9. Verwendung von Cycloalkano[b]indolsulfonamiden, die durch Heterocyclen substituiert sind, nach Anspruch 1 bis 3 zur Herstellung von Medikamenten zur Behandlung thromboembolischer Störungen, Ischämien, Arteriosklerose, Asthma und Allergien.

10. Verbindungen der allgemeinen Formel



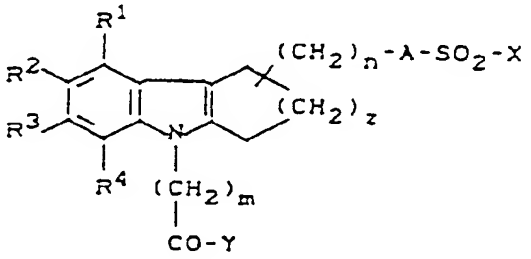
worin

R^1, R^2, R^3 und R^4	gleich oder verschieden sind und Wasserstoff, Fluor, Chlor, Trifluormethyl oder Trifluormethoxy oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoff-Atomen darstellen,
n	die Zahl 0 oder 1 darstellt,
A	die Gruppe -NH darstellt,
X	Pyridyl, Thienyl, Pyrryl, Imidazolyl, Isothiazolyl oder Thiazolyl darstellt, die gegebenenfalls durch Fluor, Chlor, Brom, Trifluormethyl, Trifluormethoxy oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoff-Atomen substituiert sind,
Y	Hydroxyl, Alkoxy mit bis zu 4 Kohlenstoff-Atomen, Phenoxy oder eine Gruppe der Formel $-NR^6R^7$ darstellt, in der R^6 oder R^7 gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoff-Atomen bezeichnen,

gegebenenfalls in isomerer Form, und deren Salze.

Patentanspruch für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung von Cycloalkano[b]indolsulfonamiden, die durch Heterocyclen substituiert sind, der allgemeinen Formel



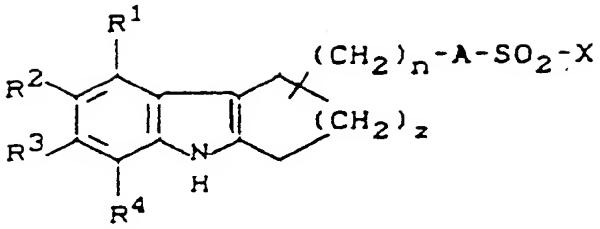
(I)

worin

R^1, R^2, R^3 und R^4	gleich oder verschieden sind und Wasserstoff, Fluor, Chlor, Trifluormethyl oder Trifluormethoxy oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoff-Atomen darstellen,
m	die Zahl 1 oder 2 darstellt,
n	die Zahl 0 oder 1 darstellt,
z	die Zahl 1 oder 2 darstellt,
A	die Gruppe -NH darstellt,
X	Pyridyl, Thienyl, Pyrryl, Imidazolyl, Isothiazolyl oder Thiazolyl darstellt, die gegebenenfalls durch Fluor, Chlor, Brom, Trifluormethyl, Trifluormethoxy oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoff-Atomen substituiert sind,
Y	Hydroxyl, Alkoxy mit bis zu 4 Kohlenstoff-Atomen, Phenoxy oder eine Gruppe der Formel $-NR^6R^7$ darstellt, in der R^6 oder R^7 gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoff-Atomen bezeichnen,

gegebenenfalls in isomerer Form,
und der Salze derselben,
dadurch gekennzeichnet, daß

[A] in dem Fall, in dem m die Zahl 2 darstellt, Verbindungen der allgemeinen Formel (II)



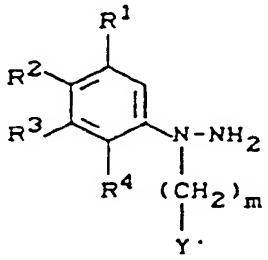
(II)

worin

R^1, R^2, R^3, R^4, A, X, n und z die oben angegebenen Bedeutungen haben,

zuerst mit Acrylnitril in inerten Lösungsmitteln zu den entsprechenden Cyanethyl-Verbindungen, gegebenenfalls in Gegenwart einer Base, umgesetzt werden und dann die Produkte nach einer gängigen Verfahrensweise zu den entsprechenden Säuren (Y = OH) hydrolysiert werden; oder

[B] Verbindungen der allgemeinen Formel (III)



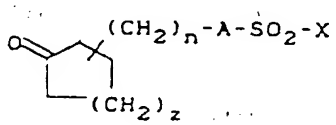
(III)

worin

R^1, R^2, R^3, R^4 und m die oben angegebenen Bedeutungen haben und

Y' Carboxyl, (C_1-C_4)-Alkoxycarbonyl oder Cyan darstellt,

direkt mit Cycloalkanonsulfonamiden der allgemeinen Formel (IV)

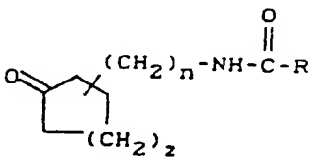


(IV)

worin

z, n, A und X die oben angegebenen Bedeutungen haben, in inerten Lösungsmitteln, gegebenenfalls in Gegenwart eines Katalysators, umgesetzt werden, oder

[C] Verbindungen der allgemeinen Formel (III) zuerst mit Verbindungen der allgemeinen Formel (IVa)



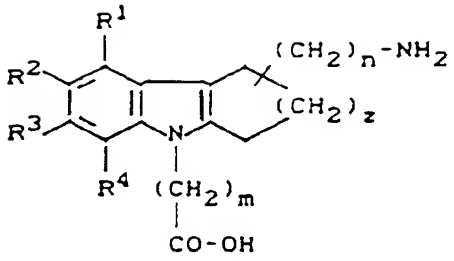
(IVa)

worin

z und n die oben angegebenen Bedeutungen haben und

R geradkettiges oder verzweigtes (C_1-C_8)-Alkyl oder Phenyl darstellt,

umgesetzt werden, wonach Hydrolyse zu Verbindungen der allgemeinen Formel (V)



(V)

erfolgt, worin

R^1, R^2, R^3, R^4, m, n und z die oben angegebenen Bedeutungen haben,

und in einem weiteren Schritt mit Sulfonylhalogeniden der allgemeinen Formel (VI)

$$Hal\text{-}SO_2\text{-}X \qquad (VI),$$

worin

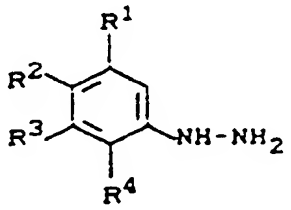
X die oben angegebenen Bedeutungen hat und

Hal Fluor, Chlor oder Brom, vorzugsweise Chlor, darstellt,

sulfoniert werden, oder

[D] in dem Fall, in dem m die Zahl 2 darstellt und A die Gruppe -NH bezeichnet,

Phenylhydrazine der allgemeinen Formel (IIIa)



(IIIa)

worin

R^1, R^2, R^3 und R^4 die oben angegebenen Bedeutungen haben,

zuerst mit den obenerwähnten Verbindungen der allgemeinen Formeln (IV) oder (IVa) und anschließend mit Acrylnitril umgesetzt werden, dann die Cyanethyl-Verbindungen zu den entsprechenden Carbonsäuren hydrolysiert werden und im Fall der Verbindungen der allgemeinen Formel (IVa) in einem weiteren Schritt mit den Verbindungen der allgemeinen Formel (VI) sulfoniert werden

und zusätzlich in den Verfahren [B] und [C] im Fall der Säuren (Y = OH) die Ester oder Nitrile nach einer gängigen Verfahrensweise hydrolysiert werden,

im Fall der Variationen der Ester (Y = Alkoxy, C_1-C_8-Phenoxy) die Säuren mit den geeigneten Alkoholen in Gegenwart eines Katalysators nach einer gängigen Verfahrensweise, gegebenenfalls in inerten Lösungsmitteln, verestert werden,

im Fall der Amide und Sulfonamide (Y = $-NR^6R^7$, $-NHSO_2-R^5$) entweder die Ester direkt oder die Säuren, nach üblicher Aktivierung, mit den Aminen oder Sulfonamiden der allgemeinen Formeln (VIIa) und (VIIb)

$$HNR^6R^7 \qquad (VIIa), \qquad NH_2\text{-}SO_2\text{-}R^5 \qquad (VIIb),$$

worin

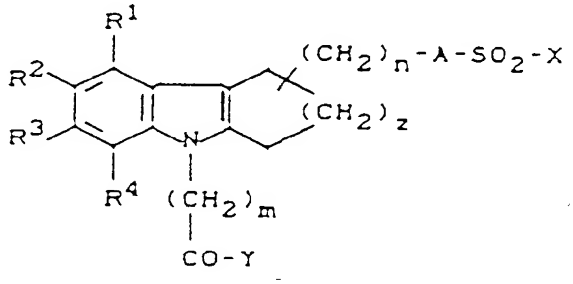
R^5, R^6 und R^7 die oben erwähnten Bedeutungen haben, gegebenenfalls in Gegenwart eines Katalysators, umgesetzt werden und

gegebenenfalls die Isomeren getrennt werden und im Fall der Herstellung der Salze mit einer geeigneten Base oder Säure umgesetzt werden.

Revendications

Revendications pour les Etats contractants suivants : DE, GB, FR, IT, NL, SE, CH, BE, AT, LU, GR, DK

1. Cycloalcano[b]indole-sulfonamides substitués par des hétérocycles, de formule

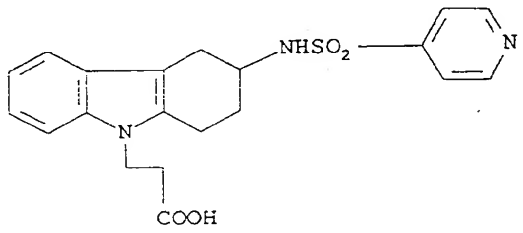


(I)

dans laquelle
R^1, R^2, R^3 et R^4 sont identiques ou différents et
- représentent l'hydrogène, le fluor, le chlore, un groupe trifluorométhyle ou trifluorométhoxy ou un groupe alkyle linéaire ou ramifié ayant jusqu'à 4 atomes de carbone,

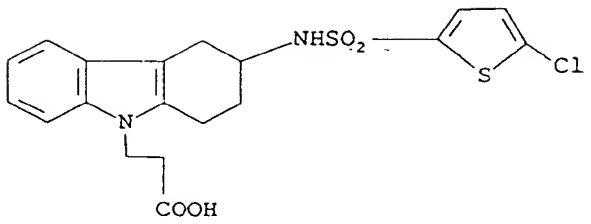
m - représente le nombre 1 ou 2,
n - représente le nombre 0 ou 1,
z - représente le nombre 1 ou 2,
A - représente le groupe -NH,
X - représente le groupe pyridyle, thiényle, pyrryle, imidazolyle, isothiazolyle ou thiazolyle, chacun étant substitué le cas échéant par du fluor, du chlore, du brome, un radical trifluorométhyle, trifluorométhoxy ou alkyle linéaire ou ramifié ayant jusqu'à 4 atomes de carbone,
Y - représente un groupe hydroxyle, alkoxy ayant jusqu'à 4 atomes de carbone, phénoxy ou un groupe de formule $-NR^6R^7$,
dans laquelle
R^6 et R^7 sont identiques ou différents et désignent l'hydrogène ou un groupe alkyle linéaire ou ramifié ayant jusqu'à 4 atomes de carbone,
sous une forme isomérique dans les cas appropriés, et leurs sels.

2. 9-(2-carboxyéthyl)-(4-pyridylsulfonamido)-1,2,3,4-tétrahydrocarbazole de formule



sous une forme isomérique dans les cas appropriés, et ses sels.

3. 9-(2-carboxyéthyl)-(5-chlorothiophène-2-yl-sulfonamido)-1,2,3,4-tétrahydrocarbazole de formule

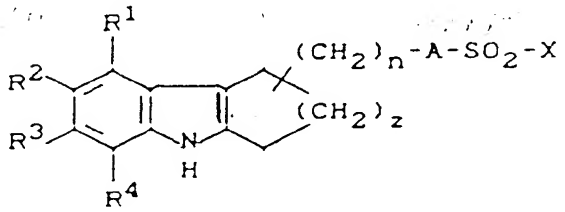


sous une forme isomérique dans les cas appropriés et ses sels.

4. Cycloalcano[b]indolesulfonamides substitués par des hétérocycles suivant les revendications 1 à 3, destinés à combattre des maladies.

5. Procédé de production des cycloalcano[b]indolesulfonamides substitués par des hétérocycles suivant les revendications 1 à 3, sous une forme isomérique dans les cas appropriés, et de leurs sels, caractérisé en ce que

[A] au cas où m représente le nombre 2, on fait réagir des composés de formule générale (II)



(II)

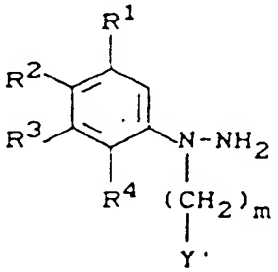
dans laquelle

R^1, R^2, R^3, R^4, A, X, n et z ont la définition indiquée dans les revendications 1 à 3,

tout d'abord avec l'acrylonitrile dans des solvants inertes pour former les composés cyanéthyliques correspondants, le cas échéant en présence d'une base, puis on les hydrolyse par un procédé usuel pour former les acides (Y=OH) correspondants,

ou par un procédé dans lequel

[B] on fait réagir des composés de formule générale (III)



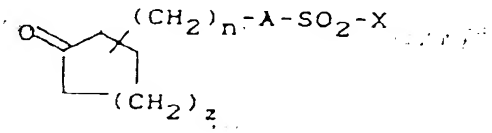
(III)

dans laquelle

R^1, R^2, R^3, R^4 et m ont la définition indiquée dans les revendications 1 à 3,

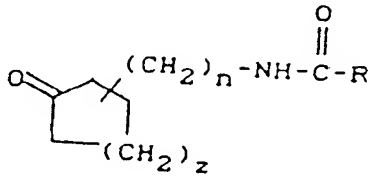
Y' - représente un groupe carboxyle, (alkoxy en C_1 à C_4)carbonyle ou cyano,

directement avec des cycloalcanone-sulfonamides de formule générale (IV)



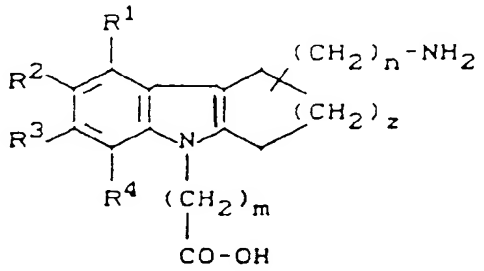
(IV)

dans laquelle
z, n, A et X ont la définition indiquée dans les revendications 1 à 3,
dans des solvants inertes, le cas échéant en présence d'un catalyseur,
ou bien
[C] on fait réagir des composés de formule générale (III) tout d'abord avec des composés de formule générale (IVa)



(IVa)

dans laquelle
z et n ont la définition indiquée dans les revendications 1 à 3,
et
R - représente un groupe alkyle en C_1 à C_8 linéaire ou ramifié ou le groupe phényle,
la réaction étant suivie d'une hydrolyse, pour former des composés de formule générale (V)

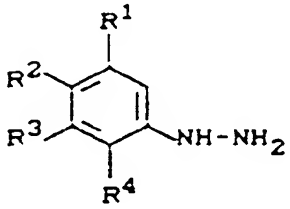


(V)

dans laquelle
R^1, R^2, R^3, R^4, m, n et z ont les définitions indiquées dans les revendications 1 à 3,
et dans une étape supplémentaire, on les sulfone avec des halogénures de sulfonyle de formule générale (VI)

$$Hal\text{-}SO_2\text{-}X \qquad (VI)$$

dans laquelle
X a la définition indiquée dans les revendications 1 à 3,
et
Hal représente le fluor, le chlore ou le brome, de préférence le chlore,
[D] ou bien dans le cas où m représente le nombre 2 et A désigne le groupe -NH
on fait tout d'abord réagir des phénylhydrazines de formule générale (IIIa)



(IIIa)

dans laquelle
R^1, R^2, R^3 et R^4 ont la définition indiquée dans les revendications 1 à 3,
avec les composés mentionnés ci-dessus de formule générale (IV) ou (IVa) puis avec l'acrylonitrile, après quoi on hydrolyse les composés cyanéthyliques en les acides carboxyliques correspon-

dants et dans le cas des composés de formule générale (IVa), on les sulfone dans une autre étape avec les composés de formule générale (VI) et en outre, dans les procédés [B] et [C], dans le cas des acides (Y=OH), on hydrolyse les esters ou nitriles par un procédé usuel,

dans le cas de la variation des esters (Y = alkoxy, C_1-C_8-phénoxy), on estérifie les acides avec les alcools appropriés en présence d'un catalyseur selon le mode opératoire usuel, le cas échéant dans des solvants inertes,

dans le cas des amides et des sulfonamides (Y = $-NR^6R^7$, $-NHSO_2-R^5$), on fait réagir les esters directement ou les acides, après activation usuelle, avec les amines ou les sulfonamides de formules générales (VIIa) et (VIIb)

HNR^6R^7 (VIIa) $NH_2-SO_2-R^5$ (VIIb)

dans lesquelles

R^5, R^6 et R^7 ont la définition indiquée ci-dessus,

le cas échéant en présence d'un catalyseur

et, lorsque cela convient, on sépare les isomères et, dans le cas de la préparation des sels, on les fait réagir avec une base ou un acide approprié.

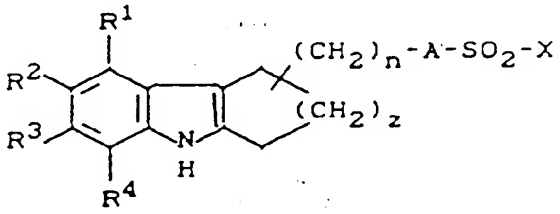
6. Médicaments contenant au moins un cycloalcano[b]indolesulfonamide substitué par des hétérocycles suivant les revendications 1 à 3.

7. Procédé de préparation d'un médicament suivant la revendication 6, caractérisé en ce que des composés suivant les revendications 1 à 3 sont mis sous une forme qui convient pour l'administration, le cas échéant à l'aide de substances auxiliaires et d'excipients.

8. Utilisation de cycloalcano[b]indolesulfonamides substitués par des hétérocycles suivant les revendications 1 à 3 pour la préparation de médicaments.

9. Utilisation de cycloalcano[b]indolesulfonamides substitués par des hétérocycles suivant les revendications 1 à 3 pour la préparation de médicaments destinés au traitement de troubles thrombo-emboliques, d'ischémies, de l'artériosclérose, de l'asthme et d'allergies.

10. Composés de formule générale



dans laquelle

R^1, R^2, R^3 et R^4 sont identiques ou différents et

- représentent l'hydrogène, le fluor, le chlore, le groupe trifluorométhyle ou trifluorométhoxy ou un groupe alkyle linéaire ou ramifié ayant jusqu'à 4 atomes de carbone

n - représente le nombre 0 ou 1,

A - représente le groupe -NH,

X - représente le groupe pyridyle, thiényle, pyrryle, imidazolyle, isothiazolyle ou thiazolyle, chacun étant substitué le cas échéant par du fluor, du chlore, du brome, un radical trifluorométhyle, trifluorométhoxy ou alkyle linéaire ou ramifié ayant jusqu'à 4 atomes de carbone,

Y - représente un groupe hydroxyle, alkoxy ayant jusqu'à 4 atomes de carbone, phénoxy ou un groupe de formule $-NR^6R^7$,

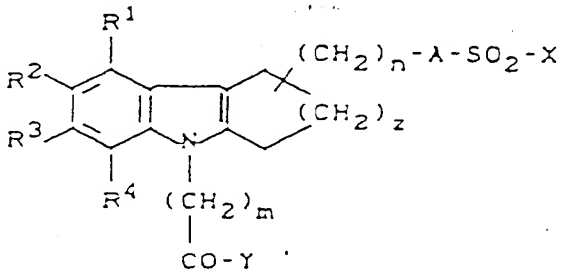
dans laquelle

R^6 et R^7 sont identiques ou différents et désignent l'hydrogène ou un groupe alkyle linéaire ou ramifié ayant jusqu'à 4 atomes de carbone,

le cas échéant sous une forme isomérique, et leurs sels.

Revendication pour l'Etat contractant suivant : ES

1. Procédé de production de cycloalcano[b]indolesulfonamides substitués par des hétérocycles, de formule générale



(I)

dans laquelle

R^1, R^2, R^3 et R^4 sont identiques ou différents et

- représentent l'hydrogène, le fluor, le chlore, un groupe trifluorométhyle ou trifluorométhoxy ou un groupe alkyle linéaire ou ramifié ayant jusqu'à 4 atomes de carbone,

m - représente le nombre 1 ou 2,

n - représente le nombre 0 ou 1,

z - représente le nombre 1 ou 2,

A - représente le groupe -NH,

X - représente le groupe pyridyle, thiényle, pyrryle, imidazolyle, isothiazolyle ou thiazolyle, chacun étant substitué le cas échéant par du fluor, du chlore, du brome, un radical trifluorométhyle, trifluorométhoxy ou alkyle linéaire ou ramifié ayant jusqu'à 4 atomes de carbone,

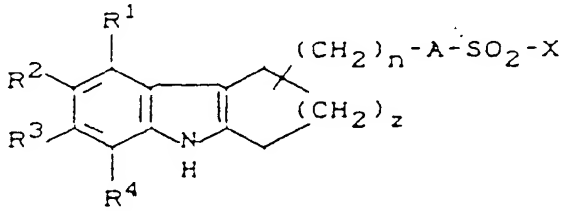
Y - représente un groupe hydroxyle, alkoxy ayant jusqu'à 4 atomes de carbone, phénoxy ou un groupe de formule $-NR^6R^7$,

dans laquelle

R^6 et R^7 sont identiques ou différents et désignent l'hydrogène ou un groupe alkyle linéaire ou ramifié ayant jusqu'à 4 atomes de carbone,

sous une forme isomérique dans les cas appropriés, et de leurs sels, caractérisé en ce que

[A] au cas où m représente le nombre 2, on fait réagir des composés de formule générale (II)



(II)

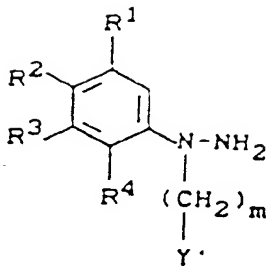
dans laquelle

R^1, R^2, R^3, R^4, A, X, n et z ont la définition donnée ci-dessus,

tout d'abord avec l'acrylonitrile dans des solvants inertes pour former les composés cyanéthyliques correspondants, le cas échéant en présence d'une base, puis on les hydrolyse par un procédé usuel pour former les acides (Y=OH) correspondants,

ou par un procédé dans lequel

[B] on fait réagir des composés de formule générale (III)



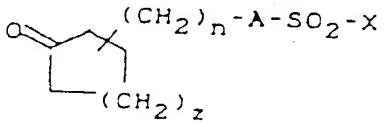
(III)

dans laquelle

R^1, R^2, R^3, R^4 et m ont la définition donnée ci-dessus,

Y' - représente un groupe carboxyle, (alkoxy en C_1 à C_4)carbonyle ou cyano,

directement avec des cycloalcanone-sulfonamides de formule générale (IV)



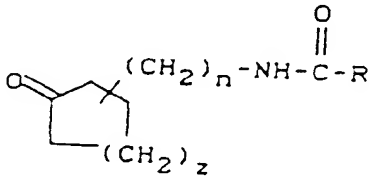
(IV)

dans laquelle

z, n, A et X ont la définition donnée ci-dessus, dans des solvants inertes, le cas échéant en présence d'un catalyseur,

ou bien

[C] on fait réagir des composés de formule générale (III) tout d'abord avec des composés de formule générale (IVa)



(IVa)

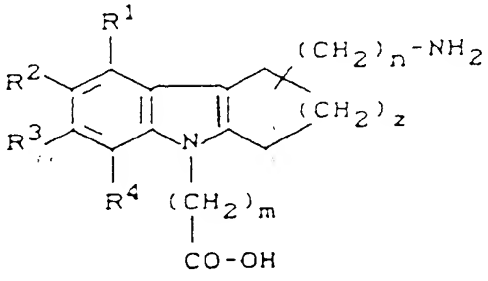
dans laquelle

z et n ont la définition donnée ci-dessus,

et

R - représente un groupe alkyle en C_1 à C_8 linéaire ou ramifié ou le groupe phényle,

la réaction étant suivie d'une hydrolyse, pour former des composés de formule générale (V)



(V)

dans laquelle

R^1, R^2, R^3, R^4, m, n et z ont les définitions données ci-dessus,

et dans une étape supplémentaire, on les sulfone avec des halogénures de sulfonyle de formule générale (VI)

$$Hal\text{-}SO_2\text{-}X \qquad (VI)$$

dans laquelle

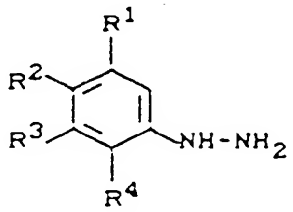
X a la définition donnée ci-dessus,

et

Hal représente le fluor, le chlore ou le brome, de préférence le chlore,

[D] ou bien dans le cas où m représente le nombre 2 et A désigne le groupe -NH

on fait tout d'abord réagir des phénylhydrazines de formule générale (IIIa)



(IIIa)

dans laquelle

R^1, R^2, R^3 et R^4 ont la définition donnée ci-dessus,

avec les composés mentionnés ci-dessus de formule générale (IV) ou (IVa) puis avec l'acrylonitrile, après quoi on hydrolyse les composés cyanéthyliques en les acides carboxyliques correspondants et dans le cas des composés de formule générale (IVa), on les sulfone dans une autre étape avec les composés de formule générale (VI) et en outre, dans les procédés [B] et [C], dans le cas des acides (Y=OH), on hydrolyse les esters ou nitriles par un procédé usuel,

dans le cas de la variation des esters (Y = alkoxy, C_1-C_8-phénoxy), on estérifie les acides avec les alcools appropriés en présence d'un catalyseur selon le mode- opératoire usuel, le cas échéant dans des solvants inertes,

dans le cas des amides et des sulfonamides (Y = $-NR^6R^7$, $-NHSO_2$-R^5), on fait réagir les esters directement ou les acides, après activation usuelle, avec les amines ou les sulfonamides de formules générales (VIIa) et (VIIb)

$$HNR^6R^7 \qquad (VIIa) \qquad NH_2\text{-}SO_2\text{-}R^5 \qquad (VIIb)$$

dans lesquelles

R^5, R^6 et R^7 ont la définition indiquée ci-dessus,

le cas échéant en présence d'un catalyseur

et, lorsque cela convient, on sépare les isomères et, dans le cas de la préparation des sels, on les fait réagir avec une base ou un acide approprié.